ANOMALOUS NUCLEOSIDES AND RELATED COMPOUNDS

XI. Amino Acid Derivatives of 6-Azauracil*

V. P. Chernetskii, I. V. Alekseeva, and A. S. Shalamai

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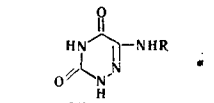
In order to obtain nontoxic biologically active aza analogs of pyrimidine, the synthesis of amino acid derivatives of 6-azauracil has been carried out: a) by the reaction of 5-bromo-6-azauracil (I) [1] with amino acid salts, and b) by the carbodiimide condensation of 5-amino-6-azauracil (II) [1] with benzyloxycarbonylamino acids.



III R = CH_2COOH;
IV R = $CHCH_3COOH$;
V R = $CHCH(CH_3)_2COOH$;
VI R = CH_2COOCH_3;
VII R = $COCH_2NHCOOCH_2C_6H_5$

We have obtained compounds III–V by boiling concentrated aqueous solutions of potassium salts of amino acids (glycine, DL-alanine, DL-valine) with I.

Table 1

Amino Acid Derivatives of 4-Azauracil

Compound	Mp, °C (decomp.)	R_f* A	R_f* B	Empirical formula	N, % found	N, % calculated	Yield, %
III	265–270	0.42	0.07	$C_5H_6N_4O_4$	29.98	30.10	42
IV	272–276	0.48	0.07	$C_6H_8N_4O_4$	28.29	27.99	40
V	268–271	0.52	0.10	$C_8H_{12}N_4O_4$	24.77	24.55	52
VI	176–179	0.48	0.47	$C_6H_9N_4O_4$	27.87	27.85	80
VII	229–231	0.42	0.35	$C_{13}H_{13}N_5O_5$	22.02	21.95	57

*A: n-butanol–acetic acid–water (5 : 2 : 3); B: n-butanol–ethanol–water (4 : 1.1 : 1.9).

Compounds III–V are colorless substances which melt at high temperatures with decomposition and are readily soluble in water and sparingly soluble in alcohols and the majority of organic solvents. When alkaline solutions of III–V are heated, the triazine ring is destroyed. The esterification of III gives VI.

Compound VII was obtained by the reaction of benzyloxycarbonylglycine with II in dioxane in the presence of dicyclohexylcarbodiimide (DCCD). When VII was subjected to alkaline hydrolysis, II and glycine were identified chromatographically.

The absorption curves of III–V in 0.1 N HCl and 0.1 N NaOH differ considerably from the curves of I and are correspondingly close to the spectra of II. In a neutral medium, the absorption maxima of III–V are shifted in the long-wave direction by 6 nm as compared with the maximum of II, apparently because of the interaction of the carboxy group of the amino acid residue with the keto group of the triazine ring. However, where the carboxy group is blocked, the absorption maxima coincide (II and VI).

*For part X, see [2].

EXPERIMENTAL

(6-Azauracil-5-yl)amino acids (III–V). In portions, 8 mM of dry potassium hydroxide was added to a solution of 8 mM of the appropriate amino acid in 6 ml of water and then, with stirring, 5.3 mole of I was gradually added. The mixture was boiled under reflux for 13 hr. After cooling, it was acidified with concentrated HCl to pH 5.5. After the formation of a crystalline mass, the contaminating I was washed out with hot ethanol. The product was crystallized from aqueous ethanol.

Methyl ester of N-(6-azauracil-5-yl)glycine (VI). With cooling to 0° C, 0.04 ml of freshly-distilled thionyl chloride was added to a suspension of 2.6 mM of III in 15 ml of absolute methanol, and the mixture was gradually heated to 60° C and kept at this temperature for another hour. The excess of methanol was distilled off in vacuum until the crystallization of the VI began. The crystals were filtered off and washed with ether. Yield 80%.

5-(Benzyloxycarbonylglycylamino)-6-azauracil (VII). With heating, 1.1 mM of II was dissolved in 30 ml of absolute dioxane. To the cooled solution was added 1.1 mM of benzoxycarbonylglycine and 1.2 mM of DCCD, and the mixture was left for a day at room temperature. The urea was filtered off, the filtrate was evaporated to dryness, and the VII was extracted with ethanol. The ethanolic solution was concentrated until the VII began to crystallize. Yield 57%.

Table 2

UV Absorption Spectra

Compound	λ_{max} in 0.1N HCl, nm	λ_{max} in 0.1N NaOH, nm	λ_{max} in water, nm
I	274	299	276
II	296	289	298
III–V	298	292	304
VI	—	—	298
VII	—	—	301*

*Solvent–ethanol.

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Zabolotnyi Institute of Microbiology and Virology
AS UkrSSR, Kiev